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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/710,444	11/10/2000	Lutz Riechmann	8654/1090	5253

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EXAMINER
STEELE, AMBER D

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 07/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/710,444	RIECHMANN ET AL.	
	Examiner	Art Unit	
	Amber D. Steele	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. The amendment received on April 10, 2006 amended claims 1-3, 8-9, and 20 and canceled claim 4.

Claims 1-3 and 5-21 are currently pending and under consideration.

Election/Restrictions

2. Claims 10 and 12 were withdrawn in the Office action mailed November 10, 2005 as being directed to a non-elected invention (please refer to section 4). However, in view of applicants' arguments and the amendments to claim 1, claims 10 and 12 are rejoined with the elected invention.

Priority

3. Receipt is acknowledged of papers (United Kingdom 9810223.9 05/13/1998 and United Kingdom 9810228.8 05/13/1998) submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

4. The priority of the present application is acknowledged as being a CON of PCT/GB99/01526 05/13/1999. In addition, foreign priority to United Kingdom 9810223.9 and United Kingdom 9810228.8 is acknowledged.

Oath/Declaration

5. The new non-executed Declaration was received which corrects the issues raised in the previous Office action.

6. Acknowledgement of applicants' intent to file a properly executed Declaration is made. However, for clarity of the record the oath or declaration is stated to be defective because the signatures of the applicants are not present. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: It was not executed in accordance with either 37 CFR 1.66 or 1.68.

Withdrawn Objections

7. The objections to the specification (sections 11 a-I of the previous Office action) are withdrawn due to the amendments to the specification.

8. The objection of claim 2 is withdrawn due to the amendment to the claim.

Withdrawn Rejections

9. The claim rejections under 35 USC § 112, first paragraph is withdrawn due to the amendments to the claims.

10. The claim rejections under 35 USC § 112, second paragraph is withdrawn due to the amendment to the claims.

11. The rejection under 35 U.S.C. 102(b) regarding Ladner *et al.* U.S. patent 5,223,409 issued June 29, 1993 is withdrawn due to the amendments to the claims.

12. The rejection under 35 U.S.C. 102(b) regarding Dower *et al.* U.S. Patent 5, 432, 018 issued July 11, 1995 is withdrawn due to the amendments to the claims.

13. The rejection under 35 U.S.C. 103(a) regarding Ladner *et al.* U.S. patent 5,223,409 issued June 29, 1993 and Smith, G. P. Science. Filamentous Fusion Phage: Novel Expression Vectors that Display Cloned Antigens on the Virion Surface. 228: 1315-1317, 1985 is withdrawn due to the amendments to the claims.

14. The rejection under 35 U.S.C. 103(a) regarding Dower *et al.* U.S. Patent 5,432,018 issued July 11, 1995 and Breitling *et al.* U.S. Patent 5,849,500 issued December 15, 1998 is withdrawn due to the amendments to the claims.

15. The rejection under 35 U.S.C. 103(a) regarding Dower *et al.* U.S. Patent 5, 432, 018 issued July 11, 1995, Breitling *et al* U.S. Patent 5,849,500 issued December 15, 1998, and Smith, G. P. Science. Filamentous Fusion Phage: Novel Expression Vectors that Display Cloned Antigens on the Virion Surface. 228: 1315-1317, 1985 is withdrawn due to the amendments to the claims.

New Objections/Rejections due to Amendments

Claim Objections

16. Claims 11 and 12 are objected to because of the following informalities: Claims 11 and 12 should be clarified to establish that only some members of the repertoire are stabilized or destabilized and only some members of the repertoire are at least partially unfolded via the denaturant. Appropriate correction is required.

17. Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 2 is dependent on claim 1 and states that the cleavable site is located within the fusion polypeptide. Claim 1 requires the limitation that the cleavable site is located within the displayed polypeptide. Therefore, claim 2 does not further limit claim 1.

18. Claim 8 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 8 is dependent on claim 1 and states that a virion that is resistant to cleavage is propagated by infection. Claim 1 requires the limitation that cleavage impairs infection therefore claim 8 does not further limit claim 1.

Claim Rejections - 35 USC § 112

19. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claims 1-3 and 5-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 USC 112, first paragraph "Written Description" requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a **written description** rejection.

Claim 1 is drawn to a method for the selection of a virus comprising (a) providing a plurality of virions encoding and displaying a fusion polypeptide with a cleavable site, (b) exposing the virus to a cleaving agent which cleaves improperly folded fusion polypeptides, and (c) propagating a virion comprising intact fusion polypeptide. The invention as claimed encompasses all known fusion proteins and all potential fusion proteins since virtually any protein can be cleaved. The claimed invention states that cleavage of the cleavable site impairs infection. The claimed invention does not include any structural information regarding the cleavage site, the location of the cleavage site in the fusion polypeptide, or the specificity of the cleaving agent. In addition, the claimed invention does not include any structural information regarding folding of the polypeptide that could prevent cleavage of any cleavage agent. The structural limitation that the cleavage site must be inaccessible to the cleaving agent due to folding or the limitation that the cleaving agent is specific for the cleavage site and not for any other location in the polypeptide is not present in the claimed invention.

The Specification teaches that the cleavage site should be absent from the virus other than at the cleavage site or inaccessible to cleavage and may be part of the coat protein (please refer to page 4, lines 19-26; pages 9, 11). In addition, the specification also teaches proteases including trypsin, chymotrypsin, thermolysin, subtilisin, Glu-C,

and Factor X as the cleaving agent (please refer to page 9). The specific cleavage residues of the proteases are listed (please refer to page 9). However, the claimed invention does not include the structural limitations of the particular residues or structural limitations regarding how the cleavage sites are made inaccessible. Therefore, one skilled in the relevant art would not reasonably conclude that the Applicants had possession of the invention as claimed since cleaving agents could be any chemical, drug, or enzyme that alters chemical bonds (e.g. cleavage) including reducing agents. Furthermore, not all cleaving agents are expected to provide similar results regarding inhibition of viral infectivity and all cleaving agents lack of impairment of infectivity may not be solely due to proper protein folding (please refer to page 15, Example 2 wherein Factor X, Arg-C, and thrombin did not lead to a loss in infectivity despite the presence of cleavage sites and the lack of a properly folded fusion polypeptide). Therefore, the method as presently claimed would not necessarily lead to the propagation of only intact fusion polypeptides dependent on the cleavage site and the cleaving agent.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was *in possession of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See page 1116.).

With the exception of the cleavage site (e.g. SEQ ID NO: 1; please refer to example 2) utilized with trypsin, thermolysin, subtilisin, Glu-C, or chymotrypsin (Example 2) as disclosed by the specification, the skilled artisan cannot envision the

entire scope of the method of claim 1 was in applicants possession. In addition, the polypeptides barnase (e.g. mutant A) and villin are the only examples of a properly folded polypeptides that make the cleavage site inaccessible and allows for viral propagation (please refer to examples 5-6). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class wherein the specification provided only the bovine sequence.

21. Claims 1-3 and 5-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of selection of a virus comprising providing a virus encoding and displaying barnase mutant A or villin with a cleavage site (e.g. SEQ ID NO: 1), exposing the virus to trypsin, thermolysin, subtilisin, Glu-C, or chymotrypsin (e.g. cleaving agents), and propagating virus comprising a polypeptide folded in a manner that makes the cleavage site inaccessible, the specification does not reasonably provide enablement for a method of selection of a virus utilizing any known or unknown cleavage site, any known or unknown cleaving agent, and any known or unknown polypeptide. The specification does not enable a person skilled in the art to make and use the invention commensurate in scope with the claim.

There are many factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement

requirement and whether any experimentation is "undue". These factors include, but are not limited to:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The level of skill in the art;
5. The level of predictability in the art;
6. The amount of direction provided by the inventor;
7. The presence or absence of working examples;
8. The quantity of experimentation necessary needed to make or use the invention based on the disclosure.

See *In re Wands* USPQ 2d 1400 (CAFC 1988):

The breadth of the claims and the nature of the invention:

The claims include any virus that can express a fusion polypeptide including surface display via phage; any cleavage site regardless of specificity for a particular cleaving agent; any cleaving agent including agents with a specific cleavage residue, agents with nonspecific cleavage residues, chemicals, enzymes, drugs, reducing agents, etc.; any known or unknown fusion polypeptide. Accordingly, the claims encompass the selection of a vast number of virus particles expressing a vast number of fusion polypeptides. Accordingly, the claim scope is unduly broad with respect to encompassed polypeptides, virions, cleavage sites, and cleaving agents.

The state of the prior art and the level of predictability in the art:

While the state of the art and level of predictability for the expression of fusion proteins in virus particles (e.g. phage display) and screening assays based on binding is high, the art is silent at the time of the disclosure with regard to correlating a decrease in viral infectivity with improper protein folding including which cleavage sites and cleaving agents would be advantageous in the method. The state of the art in July 1998 reported that not all cleaving agents produced the expected result of decreasing viral infectivity. Kristensen and Winter (Folding & Design 3: 321-328, 1998) teach that a cleavage site with several proteolytic sites was susceptible to cleavage by trypsin, thermolysin, subtilisin, Glu-C, and chymotrypsin but infectivity of the virus was not altered by Factor Xa, Arg-C, or thrombin even though potential cleavage sites were present (please refer to pg. 322). In addition, Kristensen and Winter note that several limitations to the method are present including phage must be resistant to the digestion conditions, protein must be exported to the surface, the cleavage site must be specific for a chosen protease, and the fusion protein must cleave after nicking without noncovalent attachment (pg. 324). Please also refer to Example 2 of the present specification. Furthermore, Sieber et al. (Nature Biotechnology 16: 955-960, October 1998) teach that correlating proteolytic stability with infectivity of filamentous phage is best suited to compact monomeric proteins and consideration of the phage stability and the specific protease utilized is necessary (please refer to pg. 958-959).

The level of skill in the art:

The level of skill would be high, most likely at the Ph.D. level.

The amount of direction provided by the inventor and the existence of working examples:

The specification provides examples of two fusion proteins that can be utilized to make the cleavage site inaccessible via folding, provides one cleavage site construct, and five of eight cleavage agents utilized in a control experiment would be useful for additional experimentation (examples 2, 5, and 6).

The quantity of experimentation needed to make or use the invention based on the content of the disclosure:

In light of the unpredictability surrounding the claimed subject matter, the undue breadth of the claimed invention's intended use, and the lack of adequate guidance, one wishing to practice the presently claimed invention would be unable to do so without engaging in undue experimentation. One wishing to practice the presently claimed invention would have to produce additional cleavage sites, experiment with additional denaturing conditions dependant of the stability of the naïve protein, experiment with various cleaving agents especially if agents outside the genus of proteases are utilized wherein even some of the preferred embodiment of proteases were found to be nonfunctional in the method, and take into consideration the stability of the virus utilized.

Therefore, the presently claimed invention is not enabled for the scope of the claimed method.

Conclusion

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Future Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is 571-272-5538. The examiner can normally be reached on Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ADS
June 23, 2006

PETER PARAS, JR.
PRIMARY EXAMINER

STE 1639